H, 9.35%; M^+, 166. Calc. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.5%; M, 166). τ (60 MHz; CCl_4) 3.84 (1 H, s, ArH), 5.38 (1 H, s, OH), 6.27 (3 H, s, OMe), 7.80 (3 H, s, Me), and 7.98 (6 H, s, 2 × Me).

Formylation of Methyl O-Methylrhizinonate (9).—Aluminium chloride (12.4 g) in dry ether (80 ml) was added to a stirred mixture of the substrate (9)[8] (10.2 g) in dry ether (200 ml) at 0 °C. The mixture was saturated with hydrogen chloride and set aside for 36 h. Work-up as before gave a crude product which was again subjected to the same conditions. Hydrolysis of the oily layer gave a crude product which was chromatographed over silica gel (3 × 4.5 cm) with 0—2.5% ethyl acetate–light petroleum as eluant. Early fractions afforded methyl rhizinonate (1.1 g) as plates (from methanol), m.p. 98—100° (lit.,[8] 101—102.5°). Later fractions gave *methyl 5-formyl-2-hydroxy-4-methoxy-3,6-dimethylbenzoate* (10) (800 mg), which formed needles (from light petroleum), m.p. 117—118° (Found: C, 60.3; H, 5.95%; M^+, 238. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%; M, 238), τ (60 MHz; CCl_4) −1.73 (1 H, s, OH), −0.33 (1 H, s, CHO), 6.03 and 6.20 (each 3 H, s, OMe), and 7.37 and 7.88 (each 3 H, s, Me). A sample on hydrogenation as before gave *methyl 2-hydroxy-4-methoxy-3,5,6-trimethylbenzoate* (11) as an oil (Found: M^+, 224.1035. $^{12}C_{12}{}^1H_{16}{}^{16}O_4$ requires M, 224.1049), τ (CCl_4) −1.00 (1 H, s, OH), 6.08 and 6.37 (each 3 H, s, OMe), 7.63 (3 H, s, Me), and 7.90 (6 H, s, 2 × Me).

Methyl 2,4-Dihydroxy-3,5,6-trimethylbenzoate (13).—The ester (10) (600 mg) in dry dichloromethane (20 ml) was added at −10 °C to a stirred solution of boron trichloride (1.5 g) in dry dichloromethane (40 ml). After 0.75 h at −10 °C and 2 h at room temperature the mixture was worked up in the usual way and the crude product filtered through a column of silica gel (1.5 × 2.8 cm) with 2.5—5% ethyl acetate–light petroleum as eluant. This afforded methyl 5-formyl-2,4-dihydroxy-3,6-dimethylbenzoate (12)[8] (263 mg), which was hydrogenated as before. The product (13) (227 mg, 42% overall) formed fine needles (from light petroleum), m.p. 96—97° (lit.,[8] 97—98°) (Found: C, 62.7; H, 6.7%; M^+, 210. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.7%; M, 210). τ (60 MHz; CCl_4) −1.38 and 4.84 (each 1 H, s, OH), 6.13 (3 H, s, OMe), 7.67 (3 H, s, Me), and 7.95 (6 H, s, 2 × Me).

3-Methoxy-2,5,6-trimethylphenyl 3,5-Diformyl-2,4-dihydroxy-6-methylbenzoate (*Nephroarctin*) (1).—The acid (6) (200 mg) and the phenol (8) (150 mg) were stirred for 3 h at room temperature with trifluoroacetic anhydride (3 ml) and dry toluene (8 ml). The solvents were removed and the residue was chromatographed over silica gel (1.5 × 25 cm) with 0—5% ethyl acetate–light petroleum as eluant. This gave *nephroarctin* (1) (75 mg, 23%), which formed prisms (from acetone), m.p. and mixed m.p. 199—200° (lit.,[1] 192—193°; lit.,[2] 200—201°) (Found: C, 64.3; H, 5.6%; M^+, 372. $C_{20}H_{20}O_7$ requires C, 64.5; H, 5.4%; M, 372), τ (90 MHz; $CDCl_3$) −3.85 and −3.47 (each 1 H, s, OH), −0.35 and −0.20 (each 1 H, s, CHO), 3.36 (1 H, s, ArH), 6.18 (3 H, s, OMe), 7.25 and 7.70 (each 3 H, s, Me), and 7.86 (6 H, s, 2 × Me), identical (mass and n.m.r. spectra, R_F values in three solvent systems) with an authentic sample.

3-Hydroxy-4-methoxycarbonyl-2,5,6-trimethylphenyl 3,5-Diformyl-2,4-dihydroxy-6-methylbenzoate (*Phenarctin*) (2).—Condensation of the acid (6) (228 mg) and the phenol (13) (214 mg) followed by chromatography as before gave *phenarctin* (2) (146 mg, 35%) as prisms (from acetone), m.p. and mixed m.p. 173—174° (lit.,[1] 167—168°) (Found: C, 60.5; H, 4.8%; M^+, 416. $C_{21}H_{20}O_9$ requires C, 60.6; H, 4.85%; M, 416), τ (90 MHz; $CDCl_3$) −3.86, −3.52, and −1.06 (each 1 H, s, OH), −0.36 and −0.21 (each 1 H, s, CHO), 6.03 (3 H, s, OMe), 7.26 and 7.54 (each 3 H, s, Me), and 7.82 (6 H, s, 2 × Me), identical (mass and n.m.r. spectra, R_F values in three solvent systems) with an authentic sample.

Synthesis of Compounds related to Gibberellic Acid. Part V.[1] Introduction of the Ring B Carboxy-group

By **H. J. Eli Loewenthal** * and **Shimon Schatzmiller**, Department of Chemistry, Israel Institute of Technology, Haifa, Israel

Various methods for the introduction of a carboxy-group into the benzylic position (corresponding to the ring B carboxy-group in gibberellin A_3 nor-ketone) of methyl 16,16-ethylenedioxy-3-methoxy-9α*H*-gibba-1(10),2,4-triene-4-carboxylate (1), of the corresponding 1(10),2,4,9(11)-tetraene (2), and of the corresponding 9β*H*-epimer (10b) have been explored. The best of these has been found to involve deprotonation of these acetal esters with lithium *N*-cyclohexyl-*N*-t-butylamide, followed by carboxylation, which is highly stereospecific. Experiments on simpler models are also described.

In Part IV[1] we described a rational synthesis of the acetal esters (1) and (2). The remaining problem, prior to modification of ring A on the lines previously described,[2] was the introduction of a carboxy-group into the benzylic position corresponding to C-6 † in gibberellin A_4 nor-ketone (3).

Hauser and his co-workers have shown that deprotonation at a benzylic carbon atom is facilitated by the presence in the *ortho*-position of a nitrogen function such as a benzylamine,[3] a benzamide,[4] or a sulphon-

† For nomenclature and numbering, see Part IV, footnote †.

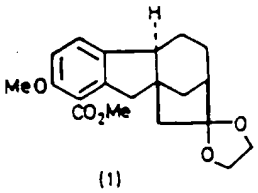
[1] Part IV, H. J. E. Loewenthal and S. Schatzmiller, *J.C.S. Perkin I*, 1975, 2149.

[3] M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, 1969, **34**, 126.

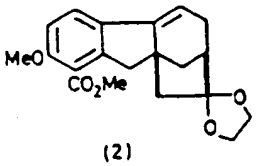
[3] R. L. Vaulx, F. N. Jones, and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 1387.

[4] R. L. Vaulx, W. H. Puterbaugh, and C. R. Hauser, *J. Org. Chem.*, 1964, **29**, 3614; R. E. Ludt, J. S. Griffith, R. N. MacGrath, and C. R. Hauser, *ibid.*, 1973, **38**, 1668.

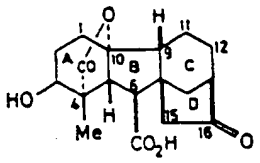
amide,[5] which appears to stabilise the carbanion formed by co-ordination with the cation. Although these authors did not describe carboxylation of their dianionic



(1)



(2)



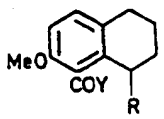
(3)

intermediates, we assumed that this approach could lead to the introduction of the desired carboxy-group into the intermediates (1) and (2) after prior conversion of the ester function into a substituted benzamide. This idea was first tried on simpler models such as the esters (4b) and (5b); and the problem was then to find a way of converting these esters directly into substituted amides, without going through the corresponding acids (4a) and (5a) and their acid chlorides, in view of the presence of the sensitive acetal grouping in compounds (1) and (2).

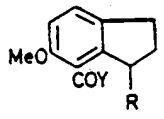
Owing to the hindered nature of the esters, direct aminolysis was unsuccessful, and this approach was rendered even more unattractive when it appeared later that amides derived from hindered amines would give better results. We then found that use of the lithium derivatives of such amines, involving the ^-NHR anion rather than merely the lone nitrogen electron pair, converted these hindered esters into substituted amides in high yield. Since this work was done a similar approach has been reported.[6,7]

Treatment of the substituted amides with 2 equiv. of n-butyl-lithium gave the expected dianions, whose carboxylation led to the expected amide acids. The position of carboxylation was clear from the formation of the *N*-t-butylimide (7a), either by treatment of the acid (4e) with acetic anhydride and sodium acetate (apparently *via* an isoimide [8]), or by displacement of methoxide ion from the ester (4f) with sodium t-pentyl oxide. Subsequent treatment with trifluoroacetic acid led to the imide (7b), but all attempts to hydrolyse this to a carboxylic acid failed. On the other hand, treatment of the indane amide acid (5e) with formic acid appeared to give directly the unsubstituted imide (8), alkaline hydrolysis of which was successful. Another example of this difference, due to differences in steric hindrance, between an indane and a tetrahydronaphthalene system, is described later.

Another approach to the problem of removing the nitrogen function once it had served its purpose was suggested by the nitrosation procedure described by White.[9] Preliminary experiments showed that the *N*-n-propylamide ester (4g) could indeed be nitrosated and the product converted into the diester (4k) *via* an acylnitrene rearrangement, but the *N*-t-butylamide esters (4f) and (5f) could not be nitrosated in the first place. Other workers in this field [10,11] have since reported success with

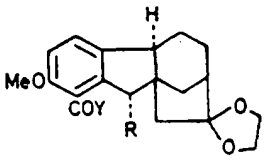


(4)



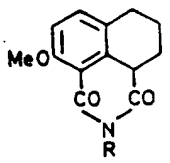
(5)

a; Y = OH, R = H
b; Y = OMe, R = H
c; Y = NHBu^t, R = H
d; Y = NHPr^n, R = H
e; Y = NHBu^t, R = CO_2H
f; Y = NHBu^t, R = CO_2Me
g; Y = NHPr^n, R = CO_2Me
h; Y = OH, R = CO_2H
i; Y = OMe, R = CO_2H
j; Y = OMe, R = CO_2Me
k; Y = OPr^n, R = CO_2Me



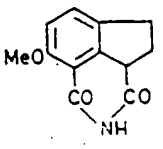
(6)

a; Y = NHBu^t, R = H
b; Y = NHBu^t, R = CO_2H
c; Y = NHBu^t, R = CO_2Me
d; Y = OMe, R = CO_2H
e; Y = OMe, R = CO_2Me
f; Y = OH, R = CO_2H



(7)

a; R = Bu^t
b; R = H



(8)

this approach, but at this point we decided to explore a more direct route.

Creger [12] has reported that treatment of *o*-toluic acid

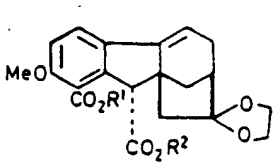
[6] H. Watanabe and C. R. Hauser, *J. Org. Chem.*, 1968, **33**, 4278.
[7] K. Yang, J. G. Cannon, and J. G. Rose, *Tetrahedron Letters*, 1970, 1791.
[7] B. Singh, *Tetrahedron Letters*, 1971, 321.
[8] W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, 1963, **28**, 2018; M. K. Hargreaves, J. G. Pritchard, and H. R. Dave, *Chem. Rev.*, 1970, **70**, 488.
[9] E. H. White and C. A. Aufdermarsch, *J. Amer. Chem. Soc.*, 1961, **83**, 1179.
[10] A. J. Baker and A. C. Goudie, *J.C.S. Chem. Comm.*, 1972, 951.
[11] H. O. House, W. E. Hanners, and E. J. Racah, *J. Org. Chem.*, 1972, **37**, 958.
[12] P. L. Creger, *J. Amer. Chem. Soc.*, 1970, **92**, 1396.

with 2 equiv. of a strong base such as n-butyl-lithium leads to a stable dianion, alkylation of which proceeds on the methyl group. Following up this idea, we treated the acid (4a) with butyl-lithium; carboxylation then led in high yield to the dicarboxylic acid (4h), which could be converted into a cyclic anhydride. However, in the case of the corresponding indanecarboxylic acid (5a), more closely related to compounds (1) and (2), the alternative nucleophilic addition of butyl-lithium to the carboxylate carbonyl group to give an aromatic ketone [13] reduced the yield of the dicarboxylic acid (5h) considerably.

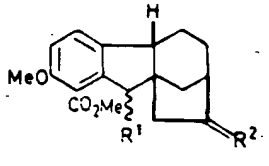
We then attempted the deprotonation and carboxylation of the methyl esters (4b), (1), and (2). For this a base such as butyl-lithium is evidently unsuitable and a hindered base of the lithium dialkylamide type was required, as suggested by the work of Rathke.[14] Various such bases were tried: employment of the lithium derivatives of di-isopropylamine,[15] *N*-cyclohexylisopropylamine,[14] and even the supposedly highly hindered 2,2,6,6-tetramethylpiperidine [16] led to an appreciable amount of nucleophilic addition to the ester carbonyl group, *i.e.* the very reaction which we have described above for the conversion of hindered esters into hindered substituted amides. Eventually the use of the lithium derivative of *N*-cyclohexyl-t-butylamine [17] led to success, and yields of over 70% in the preparation of the half-esters (4i), (6d), and (9a) were realised.

In the case of the latter two, the reaction was highly stereospecific (*cf.* ref. 11), the configuration of the carboxy-group being the one known in these systems [18] to be the thermodynamically more stable, in which it is *trans* to the two-carbon bridge. However this is ultimately the undesired configuration (see structure (3)). In addition, and more problematically, compound (6d) has the undesired 9α*H*-configuration.

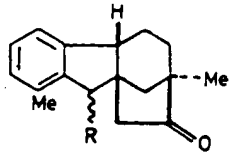
However, in the unsaturated compound (9a) the 6α-carboxy-group was expected, from past analogy,[19] to direct hydrogenation of its double bond from the opposite β-side and thus give the desired 9β*H*-configuration; indeed hydrogenation of the derived diester (9b) led to a single compound (10c), different from its epimer (6e). The dimethyl ester (10c) could then be epimerised, with methanolic sodium methoxide,[18] to give (after re-esterification), as hoped, the diester (10d) having the 9β*H*,6β-configuration in good yield (raised under conditions where hydrolysis followed epimerisation after addition of water).



(9)
a; R^1 = Me, R^2 = H
b; R^1 = R^2 = Me



(10)
a; R^1 = H, R^2 = O
b; R^1 = H, R^2 = O·CH_2·CH_2·O
c; R^1 = α – CO_2Me, R^2 = O·CH_2·CH_2·O
d; R^1 = β – CO_2Me, R^2 = O·CH_2·CH_2·O



(11)
a; R = α – CO_2Me
b; R = β – CO_2Me

Confirmation of the stereochemical course of this sequence could then be obtained beginning with the 9β*H*-ketone (10a), whose stereochemistry had been established through its synthesis by Baker [10] by a different route, and which had been obtained by us (see Part IV) as a by-product in the production of its 9α*H*-epimer. Its acetal (10b) was subjected to the same carboxylation sequence as its 9α*H*-epimer (1) to give, once again stereospecifically, the same diester (10d) as obtained through the epimerisation sequence.

The high degree of stereospecificity in the carboxylation of the acetal esters (1), (2), and (10b) is surprising, and it is difficult to provide an explanation to fit all three cases. First, the fact that the configuration of the intro-

[13] M. J. Jorgenson, *Org. Reactions*, 1970, **18**, 1.
[14] M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, 1971, **93**, 2318.
[15] M. Hamell and R. Levine, *J. Org. Chem.*, 1950, **15**, 162.
[16] R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, 1973, **95**, 582.
[17] G. Girault-Vexlearschi, *Bull. Soc. chim. France*, 1956, 582 (this paper was not abstracted by *Chemical Abstracts* and has thus escaped attention).
[18] J. F. Grove and T. P. C. Mulholland, *J. Chem. Soc.*, 1960, 3007.
[19] J. F. Grove, J. MacMillan, T. P. C. Mulholland, and W. B. Turner, *J. Chem. Soc.*, 1960, 3049.

duced carboxy-group in the products (6d), (9a), and (10d) is also the thermodynamically stable one cannot be the reason, since the initial product is the carboxylate ion, equilibration of which cannot be expected under the conditions used. Second, the relatively slight difference in steric hindrance to carboxylation from either side in all three cases cannot by itself account for the extent of stereospecificity. There remains the possibility of a stereoelectronic factor:[20] that the C-6 carbanion formed preferentially is the one most stabilised by orbital overlap with the aromatic ring by being most nearly orthogonal to it, and its configuration should resemble that of the carboxy-group which is introduced. Dreiding models show that this is indeed the case with products (6d) and (9a), but not with (10d) unless ring C in the latter has the more strained chair form. Compound (10d) is sterically similar to methyl epiallogibberate, which has been reported to be likewise resistant to epimerisation at C-6, although, as judged from models, there is little to choose between a 6α- or a 6β-configuration on steric grounds.[18]

In this connection the ^{1}H n.m.r. chemical shifts of the C-6 protons of the acetal diesters (see Table) are of interest. The recent conclusions by Baker and his co-workers[21] on the dependence of these on the stereochemistry at C-9 are difficult to apply here. In the diesters (6e) and (10d) the shifts are almost identical. One could conclude that they are governed by the torsion angle between the C(6)–H bond and the plane of the aromatic ring; however, in comparing the diesters (10d) and (10c) one finds a considerable downfield shift (0.5 p.p.m.) for the latter. This is the opposite to what one might expect from assuming that in (10d) the C-6 methoxycarbonyl group is nearly orthogonal to the plane of the benzene ring. A similar relationship has been reported (without comment)[22] for methyl gibberate (11a) and its epimer (11b) (mirror images shown for comparison), in which the protons at the same position exhibit δ 4.15 and 3.73, respectively; this shows, incidentally, that possible shielding or deshielding effects by the aromatic ester carbonyl groups in our compounds cannot be of much importance.

100 MHz ^{1}H N.m.r. spectra and assignments for tetracyclic acetal diesters (δ values; solvent $CDCl_3$)

Compd.	H-1 [a]	H-2 [a]	MeO-3	CO_2Me-4	H-6	CO_2Me-6	H-9	H-11
(6e)	6.80	7.15	3.80	3.80	3.75	3.66	3.22 (m)	5.82 (t)
(9b)	6.92	7.50	3.87	3.84	4.03	3.65		
(10c)	6.88	7.18	3.82	3.77	4.28	3.69	3.00 (m)	
(10d)	6.86	7.20	3.82	3.82	3.78	3.62	3.35 (m)	

[a] d, J 7—9 Hz.

EXPERIMENTAL

General details are as described for Part IV.[1] Dry tetrahydrofuran was prepared by distillation from potassium under argon in an apparatus incorporating a graduated receiver with a three-way Teflon stopcock from which the solvent could either be dispensed or recirculated to the distillation flask.

5,6,7,8-Tetrahydro-2-methoxy-1-naphthoic Acid (4a).—The following procedure is an improvement over that reported.[1] A suspension of 2-methoxy-1-naphthoic acid (20.2 g) and rhodium–palladium on carbon[23] (2 g) in methanol (90 ml), acetic acid (5 ml), and water (5 ml) was shaken under hydrogen at 50—35 lb in^{-2} until uptake was 110% of theoretical (2.5 h). Filtration, removal of solvents, and recrystallisation from cyclohexane gave the *acid* (18.5 g, 88%), m.p. 150—151° (lit.,[2] 148—149°). Its *methyl ester* (4b), prepared by using ethereal diazomethane, had m.p. 47—48° (from pentane at −20 °C) (Found: C, 71.0; H, 7.25. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%).

5-Methoxyindane-4-carboxylic Acid (5a).—Methyl 5-methoxy-1-oxoindane-4-carboxylate (2.20 g) was hydrogenated at atmospheric pressure in ethyl acetate–acetic acid (4 : 1; 20 ml) over palladium on carbon (from prehydrogenated palladium hydroxide) (20%; 0.2 g) until the theoretical amount was absorbed (24 h). Filtration, removal of solvent, and distillation at 130—140° C and 0.1 mmHg gave the *methyl ester* (5b), which crystallised from pentane at −20 °C in 83% yield; m.p. 42.5—43° (Found: C, 69.85; H, 6.85. $C_{12}H_{14}O_3$ requires C, 69.9; H, 6.85%). Prolonged hydrolysis (10% KOH at reflux) gave the *acid*, m.p. 135—135.5° (from chloroform–tetrahydrofuran) (Found: M^+, 192.0793. $C_{11}H_{12}O_3$ requires M, 192.0786). No satisfactory combustion analysis figures were obtained.

Preparation of N-Substituted Amides from Esters; General Procedure.—To a solution of the amine (distilled from calcium hydride; 30 mmol) in dry tetrahydrofuran (5—10 ml) was added n-butyl-lithium in hexane (11 mmol) at 0 °C, followed by the ester as a solid or dissolved in a minimal amount of dry tetrahydrofuran. After stirring at 0 °C for 10 min, the mixture was carefully neutralised with acetic acid, water was added, and the product was isolated with ether–chloroform and then recrystallised from dichloromethane–hexane. The following were thus obtained: *5,6,7,8-tetrahydro-2-methoxy-N-t-butylnaphthalene-1-carboxamide* (4c) (90%), m.p. 98—99°, $\nu_{max.}$ 1 100, 1 595, 1 660, and 3 430 cm^{-1}, δ 1.42 (9 H, s, Bu^t) (Found: C, 73.55; H, 8.7; N, 5.6. $C_{16}H_{23}NO_2$ requires C, 73.55; H, 8.85; N, 5.35%); *5,6,7,8-tetrahydro-2-methoxy-N-propylnaphthalene-1-carboxamide* (4d) (87%), m.p. 105—106°, $\nu_{max.}$ 1 080, 1 590, 1 650, and 3 430 cm^{-1} (Found: C, 73.0; H, 8.65; N, 5.7. $C_{13}H_{21}NO_2$ requires C, 72.85; H, 8.55; N, 5.65%); *5-methoxy-N-t-butylindane-4-carboxamide* (5c) (70%), m.p. 76—77°, $\nu_{max.}$ 1 600, 1 660, and 3 430 cm^{-1} (Found: C, 72.75; H, 8.3; N, 5.7. $C_{15}H_{21}NO_2$ requires C, 72.85; H, 8.55; N, 5.65%); *16,16-ethylenedioxy-3-methoxy-N-t-butyl-9αH-gibba-1(10),2,4-triene-4-carboxamide* (6a) (87%), m.p. 149—150°, $\nu_{max.}$ 1 070, 1 600, 1 660, and 3 420 cm^{-1}, δ 1.48 (9 H, s, Bu^t), 3.00 (2 H, s, H$_2$-6), 3.86 (7 H, s, MeO and acetal), 6.72 (1 H, d, J 7 Hz, H-1), and 7.04 (1 H, d, J 7 Hz, H-2).

Carboxylation of Amides; General Procedure.—To a solution of the amide (2.2 mmol) in dry tetrahydrofuran (5—10

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ml) at −50 °C under argon was added n-butyl-lithium in hexane (5 mmol). The deep red solution was stirred at −10 °C for ½ h, after which it was quickly transferred under argon pressure through a twice-bent tube into a stirred suspension of an excess of solid carbon dioxide in ether. The latter was stirred until it reached room temperature, water was added, and the aqueous phase was separated and extracted with dichloromethane. It was then acidified to pH 5 at 0° and the acidic product was isolated with chloroform. Removal of solvent was followed by drying under high vacuum (to remove traces of valeric acid); crystallisation from dichloromethane–hexane gave the amide acids. In some cases these were characterised as their methyl esters, formed with diazomethane. The following were thus obtained: 1,2,3,4-*tetrahydro*-7-*methoxy*-8-*t*-*butylcarbamoyl*-1-*naphthoic acid* (4e) (90%), m.p. 153—154°, $\nu_{max.}$ 1 620, 1 730, 2 600, and 3 420 cm^{-1} (Found: C, 66.7; H, 7.35; N, 4.65. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%) [*methyl ester* (4f), m.p. 129.5—130° (Found: C, 67.95; H, 7.85; N, 3.95. $C_{18}H_{25}NO_4$ requires C, 67.7; H, 7.9; N, 4.4%)]; *methyl* 1,2,3,4-*tetrahydro*-7-*methoxy*-8-*propylcarbamoyl*-1-*naphthoate* (4 g) (80%), m.p. 100—101°, $\nu_{max.}$ 1 600, 1 650, 1 730, and 3 430 cm^{-1} (Found: C, 66.9; H, 7.55; N, 4.6. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%); 6-*methoxy*-7-*t*-*butylcarbamoylindane*-1-*carboxylic acid* (5e) (74%), m.p. 153—154°, $\nu_{max.}$ 1 610, 1 730, 2 250, and 3 400 cm^{-1} (Found: C, 65.95; H, 7.1; N, 4.95. $C_{16}H_{21}NO_4$ requires C, 65.95; H, 7.25; N, 4.8%) [*methyl ester* (5f), m.p. 88—90° (Found: C, 67.1; H, 7.4; N, 4.6. $C_{17}H_{23}NO_4$ requires C, 66.85; H, 7.6; N, 4.6%)]; 16,16-*ethylenedioxy*-3-*methoxy*-4-*t*-*butylcarbamoyl*-9α*H*-*gibba*-1(10),2,4-*triene*-6α-*carboxylic acid* (6b) (62%) (30% starting material recovered), m.p. 214—216°, $\nu_{max.}$ 1 612, 1 735, 2 550, and 3 410 cm^{-1} (Found: C, 66.85; H, 7.15; N, 3.2. $C_{24}H_{31}NO_6$ requires C, 67.1; H, 7.3; N, 3.25%) [*methyl ester* (6c), m.p. 198—200°, δ 1.4 (9 H, s, Bu^t), 3.75 (3 H, s), 3.90br (7 H, s), 4.18 (1 H, s), 6.80 (1 H, d, *J* 9 Hz), and 7.20 (1 H, d, *J* 9 Hz); alkaline hydrolysis of this gave the foregoing amide acid without evidence of epimerisation].

1,2,3,4-*Tetrahydro*-7-*methoxy*-N-*t*-*butyl*-1,8-*naphthalimide*, (7a).—(*a*) The amide acid (4e) (5.43 g) was dissolved in acetic anhydride (15 ml), anhydrous sodium acetate (1.7 g) was added, and the mixture was stirred at 100 °C for 1 h. An initial red colour faded. Methanol (20 ml) was added, the mixture was allowed to cool, and the solvents were removed *in vacuo*. The product was isolated with ether–dichloromethane and crystallised from di-isopropyl ether at 0 °C and then from dichloromethane–hexane to give the *imide* (3.09 g), m.p. 120—121°, $\nu_{max.}$ 1 730, 1 680, and 1 590 cm^{-1}, δ 1.64 (9 H, s), 3.64 (1 H, m), 3.92 (3 H, s), 6.86 (1 H, d, *J* 8 Hz), and 7.24 (1 H, d, *J* 8 Hz) (Found: C, 71.2; H, 7.1; N, 4.9. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.35; N, 4.85%).

(*b*) The amide ester (4f) (3.70 g) was dissolved in dry benzene (100 ml), the solution was cooled under argon, and a solution of sodium t-pentyl oxide in toluene (1.57M; 17.75 ml, 2.4 equiv.) was added with stirring. The whole was left at room temperature overnight during which sodium methoxide was precipitated. Water was added, the organic layer was separated and dried, and the solvents were removed. Several recrystallisations of the residue gave the imide (2.42 g), identical with the product from (*a*). The use of sodium or lithium bistrimethylsilylamide in benzene led to inferior results.

1,2,3,4-*Tetrahydro*-7-*methoxy*-1,8-*naphthalimide* (7b).—The foregoing t-butylimide (3.09 g) was dissolved in trifluoroacetic acid (15 ml) and the solution was left at room temperature overnight, after which it was concentrated *in vacuo*. Water was added and the product was filtered off. Recrystallisation from aqueous acetic acid gave the *imide* (2.37 g), m.p. 191.5—192°, $\nu_{max.}$ (KBr) 3 180, 3 060, 2 860, 1 710sh, 1 690, and 1 580 cm^{-1} (Found: C, 67.4; H, 5.65; N, 6.1. $C_{13}H_{13}NO_3$ requires C, 67.5; H, 5.65; N, 6.05%). All attempts to hydrolyse this compound to the dicarboxylic acid (4h) by heating under reflux with 10% sodium hydroxide resulted in no change.

Experiments on Nitrosation of the Amide Esters (4f *and* g).—The compound (1.5 mmol) was dissolved in pyridine (3 ml), acetic acid (1 ml), and acetic anhydride (1 ml), the solution was cooled to 0 °C, and a solution of dinitrogen tetraoxide in acetic acid–acetic anhydride was added until there was a permanent positive reaction to starch–iodide. Water was added, the product was isolated with carbon tetrachloride, and the solution was examined in the i.r. for the appearance of the N–NO absorption (1 490 cm^{-1}) and the absence of amide bands (1 660 and 3 400 cm^{-1}). In the case of (4g) reaction was complete (but incomplete when nitrosyl chloride was used) [for conversion of the product into the dicarboxylic acid (4h) see below]; in the case of (4f) no nitrosation had occurred.

1,2,3,4-*Tetrahydro*-7-*methoxy*-1,8-*naphthalic Acid* (4h).—(*a*) To a solution of the acid (4a) (1.91 g) in dry tetrahydrofuran (35 ml) at −20 °C under argon was added dropwise and with stirring a solution of n-butyl-lithium in hexane (1.95M). The white solid formed initially dissolved after 1 mol. equiv. of the reagent had been added. After addition of a total of 10.5 ml (10% excess over 2 mol. equiv.) the red solution was stirred at −20 °C for 0.75 h. and then transferred under argon pressure into an excess of solid carbon dioxide in ether. After the suspension reached room temperature it was concentrated *in vacuo*, the residue was dissolved in water, and the solution was washed with ether–benzene and then acidified to pH 5 with solid sodium hydrogen sulphite. Isolation of the product with chloroform and recrystallisation from acetone–benzene–cyclohexane gave the *dicarboxylic acid* (1.88 g, 81%), m.p. 157—157.5° (Found: C, 62.75; H, 5.8. $C_{13}H_{14}O_5$ requires C, 62.4; H, 5.65%).

(*b*) The amide ester (4g) was nitrosated as above, and the dried carbon tetrachloride solution of the product was heated under reflux overnight after addition of a trace of sodium carbonate. Chromatography of the product on Florisil gave a fraction (216 mg) which was distilled at 160—180 °C and 0.2 mmHg; this was apparently the *n-propyl methyl ester* (4k); its alkaline hydrolysis gave, after recrystallisation, the dicarboxylic acid, identified by m.p. and mixed m.p.

Treatment of the dicarboxylic acid (500 mg) under reflux in tetrahydrofuran (10 ml) with dicyclohexylcarbodi-imide (400 mg) for 20 h, filtration, removal of solvent, and recrystallisation from dichloromethane–hexane gave the derived *anhydride* (410 mg), m.p. 146—148°, $\nu_{max.}$ 1 585, 1 605, 1 760, and 1 810 cm^{-1} (Found: C, 67.25; H, 5.5. $C_{13}H_{12}O_4$ requires C, 67.25; H, 5.2%).

The dicarboxylic acid (5.0 g) was esterified by the method of Clinton and Laskowski.[24] The crude product was treated with dioazomethane to complete esterification and the resulting diester was dissolved in methanol (25 ml). To this solution, heated to reflux, sodium hydroxide (N; 20.7 ml)

[24] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, 1948, **70**, 3135.

was added dropwise, after which heating was continued for 0.5 h, methanol was removed, water was added, and the solution was acidified to pH 5 with solid sodium hydrogen sulphite. Isolation with chloroform and recrystallisation from dichloromethane–hexane gave the *half-ester* (5i) (4.07 g), m.p. 139—139.5° (Found: C, 63.6; H, 6.0. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%).

6-*Methoxyindane*-1,7-*dicarboxylic Acid* (5h).—(*a*) The acid (5a) (500 mg) was carboxylated exactly as described for (4a). Part of the initially formed solid did not dissolve and the red colour was less intense. Work-up as described for (4a) gave an acidic fraction (459 mg) which after several recrystallisations from benzene and then from acetone–benzene afforded the *dicarboxylic acid* (200 mg), m.p. 158—158.5° (Found: C, 61.2; H, 5.1. $C_{12}H_{12}O_5$ requires C, 61.0; H, 5.1%). Addition of 1 mol. equiv. of hexamethylphosphoric triamide before carboxylation did not improve the yield. The neutral portion from this reaction (277 mg) showed a strong i.r. band at 1 685 cm^{-1} (aromatic ketone).

Treatment of the dicarboxylic acid with ethereal diazomethane gave the *dimethyl ester* (5j) as an oil, which distilled at 150 °C and 0.1 mmHg (Found: C, 63.95; H, 6.0. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%).

(*b*) The amide acid (5e) (400 mg) was heated in formic acid (2 ml) at 100 °C for 4 h, after which the solvent was removed *in vacuo*. Addition of water gave a solid (350 mg) which was evidently the imide (8), $\nu_{max.}$ (KBr) 3 180, 3 080, 2 840, 1 710 sh, 1 690, and 1 590 cm^{-1}. This (250 mg) was heated under reflux with potassium hydroxide (0.5M; 5 ml) overnight. Acidification, isolation with ether–tetrahydrofuran (4 : 1), and crystallisation from cyclohexane gave the dicarboxylic acid (200 mg), m.p. and mixed m.p. 156—158°.

N-Cyclohexyl-t-butylamine.—This was prepared from *N*-t-butylformamide, cyclohexanone, and formic acid as described previously.[17] The crude product (b.p. 79—83° at 28 mmHg) was found by g.l.c. (3% SE-30 on Varaport 30; 120 °C) to contain the starting amide as an impurity; this could be removed by stirring overnight with sodium hydroxide (20% w/v), followed by careful fractionation (spinning-band column); b.p. 81.5—83° at 28 mmHg (lit.,[25] 81—82° at 23 mmHg).

Note on the preparation of N-t-butylformamide. Contrary to usually reliable sources[20,27] there is no exothermic reaction on adding ethyl formate to t-butylamine and it is necessary to heat the mixture under reflux for at least 3 days (internal temperature rising to 95 °C) and not for 2 h.

A stock solution of the lithium derivative of this amine could be prepared by adding n-butyl-lithium in hexane (2.05M; 50 ml) to the amine (16.85 g, 20.3 ml) in dry benzene (30 ml) under argon with stirring and cooling. The resulting solution was 1.0 ± 0.1M in lithium and could be stored at room temperature for up to 2 months if rigorously protected from moisture and air.

Carboxylation of the Ester (4b).—The ester (4.43 g) was dissolved in dry tetrahydrofuran (50 ml) containing hexamethylphosphoric triamide (3.5 ml), and the solution was cooled to −15 °C under argon. The stock solution of lithium *N*-cyclohexyl-*N*-t-butylamide (23 ml; 10% excess) was then added and the red solution was stirred at −15° for 5 min, then transferred under argon pressure into a suspension of solid carbon dioxide in ether. After room temperature had been reached the solvents were removed, the residue was dissolved in water, and the solution was extracted several times with chloroform to remove hexamethylphosphoric triamide.[28] These extracts were then back-extracted twice with potassium carbonate (1.3N; 10 ml). The combined alkaline extracts were acidified at 0 °C to pH 5 with sodium hydrogen sulphite and the product was isolated with dichloromethane. Crystallisation from dichloromethane–hexane gave the half-ester (4i) (4.32 g, 81.5%), m.p. 139—139.5°, identical with the product obtained from the dicarboxylic acid (4h) (see above).

Carboxylations of Compounds (1) *and* (2).—These were conducted essentially as described for (4b), except that a larger excess of the base (35% over theoretical) was employed and that the products were isolated with chloroform containing 7% tetrahydrofuran. The following products were thus obtained.

16,16-*Ethylenedioxy*-3-*methoxy*-4-*methoxycarbonyl*-9α*H*-*gibba*-1(10),2,4-*triene*-6α-*carboxylic acid* (6d) (71%) had m.p. 214—214.5° (from dichloromethane–di-isopropyl ether), $\nu_{max.}$ (KBr) 1 071, 1 139, 1 239, 1 600, and 1 710 cm^{-1} (Found: C, 64.9; H, 6.25. $C_{21}H_{24}O_7$ requires C, 64.95; H, 6.25%). Treatment with diazomethane in tetrahydrofuran gave the *dimethyl ester* (6e), m.p. 187—188°, $\nu_{max.}$ 1 015, 1 095, 1 600, 1 725, and 1 735sh cm^{-1} (Found: C, 65.3; H, 6.25. $C_{22}H_{26}O_7$ requires C, 65.65; H, 6.5%). Alkaline hydrolysis of either the diester or of the half-ester by heating under reflux overnight with potassium hydroxide (N; containing 10% dioxan) followed by careful acidification to pH 4 at 0 °C, isolation with chloroform containing 20% tetrahydrofuran, and recrystallisation from tetrahydrofuran–benzene gave the dicarboxylic acid (6f), double m.p. 175—180 and 239—242°, which contained benzene of crystallisation [as evident from its n.m.r. spectrum; solvent $(CD_3)_2SO$] which was retained after drying at 80 °C and 0.05 mmHg, and for which no satisfactory analytical results were obtained. Re-esterification with diazomethane in tetrahydrofuran gave the diester (6e) (m.p. and mixed m.p.) in quantitative yield.

Careful t.l.c. examination of the diester (6e) obtained by esterification of the total crude carboxylation product did not reveal the presence of an epimer.

16,16-*Ethylenedioxy*-3-*methoxy*-4-*methoxycarbonylgibba*-1(10),2,4,9(11)-*tetraene*-6α-*carboxylic acid* (9a) (81%) had m.p. 230° (decomp.) (from tetrahydrofuran–cyclohexane) (Found: C, 65.25; H, 5.55. $C_{21}H_{22}O_7$ requires C, 65.25; H, 5.75%). In this case the solution of the carbanion prior to carboxylation had a purple colour. The corresponding *dimethyl ester* (9b) had double m.p. 145 and 180—181° (Found: C, 66.1; H, 6.1. $C_{22}H_{24}O_7$ requires C, 66.0; H, 6.05%). Alkaline hydrolysis of this as for the diester (6e), followed by re-esterification, gave back the diester without change. Examination of the total carboxylation product did not reveal the presence of an epimer.

Dimethyl 16,16-*Ethylenedioxy*-3-*methoxy*-9β*H*-*gibba*-1(10),-2,4-*triene*-4,6α-*dicarboxylate* (10c).—The unsaturated dimethyl ester (9b) (1.49 g) dissolved in methyl acetate (12 ml) and methanol (10 ml) was hydrogenated at atmospheric pressure over palladium on calcium carbonate (prehydrogenated; 5%; 600 mg). The theoretical amount was absorbed in 20 min. Filtration, removal of solvents, and passage in benzene–dichloromethane through Florisil (1.5 g), followed by recrystallisation from dichloromethane–hexane, gave the

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9βH,6α-*diester* (1.37 g, 91.5%), m.p. 146.5—147° (Found: C, 65.7; H, 6.45. $C_{22}H_{28}O_7$ requires C, 65.65; H, 6.5%). On t.l.c. this epimer was considerably more polar than the diester (6e).

Dimethyl 16,16-*Ethylenedioxy*-3-*methoxy*-9βH-*gibba*-1(10),-2,4-*triene*-4,6β-*dicarboxylate* (10d).—(*a*) The diester (10c) (1.164 g) was suspended in dry methanol (12 ml) and methanolic sodium methoxide (2.8M; 1.19 ml) was added. The solution was heated under reflux under argon for 8 h, after which water (3.0 ml) was added and heating was continued for another 3 h. The methanol was removed *in vacuo*, the residue was acidified with sodium hydrogen sulphite, and the product was isolated with chloroform and re-esterified with diazomethane. The crude product was passed in benzene–dichloromethane through alumina (2 g), then recrystallised twice from dichloromethane–cyclohexane to give the 9βH,6β-*diester* (745 mg), m.p. 173°; the analytical sample had m.p. 178—178.5° (Found: C, 65.4; H, 6.5. $C_{22}H_{28}O_7$ requires C, 65.65; H, 6.5%). On t.l.c. this diester was indistinguishable from its 9αH,6α-epimer (6c).

(*b*) The ketone (10a) (see Part IV [1]) (2.6 g) was acetalised by the ethylene glycol–boron trifluoride–ether complex method [1] to give *methyl* 16,16-*ethylenedioxy*-3-*methoxy*-9βH-*gibba*-1(10),2,4-*triene*-4-*carboxylate* (10b) (2.0 g) (after several recrystallisations from methanol), m.p. 109—113° (Found: C, 69.5; H, 6.9. $C_{20}H_{24}O_5$ requires C, 69.75; H, 7.0%). This acetal ester (1.6 g) was carboxylated exactly as described for its 9α*H*-epimer (1) (see above), and the acidic product from this reaction (1.63 g) was esterified with diazomethane. The product was recrystallised from dichloromethane–cyclohexane to give the diester (10d) (1.142 g), m.p. and mixed m.p. 178—179°. T.l.c. of the mother liquors revealed no trace of the epimeric diester (10c).

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Syntheses towards the Carbohydrate Moiety of Lincomycin

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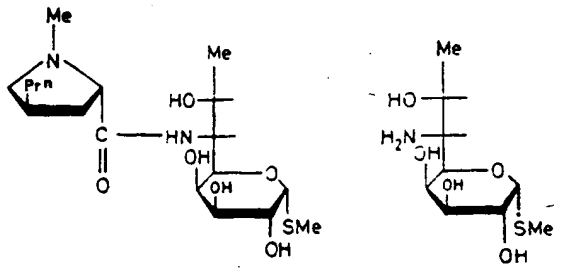
A key intermediate in the synthesis of the antibiotic lincomycin, 6-acetamido-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*erythro*-D-*galacto*-octopyranose (10), has been synthesised from *cis*-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-nitro-α-D-*galacto*-oct-6-enose (3). The amino-group at C-6 was introduced by two different procedures.

LINCOMYCIN (1), an antibiotic produced by *Streptomyces lincolnensis* var. *lincolnensis*,[1] has been shown to be effective against most of the common gram-positive pathogens. A number of syntheses towards the carbohydrate moiety of the antibiotic have been published,[2-7] and a total synthesis of the sugar portion, methyl 6-amino-6,8-dideoxy-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside (2), has been described.[8] A synthesis of the amino-acid component of lincomycin has been reported [9,10] and compound (2) was acylated [11] with this amino-acid to produce the antibiotic (1).

The starting material in the present synthesis, *cis*-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-nitro-α-D-*galacto*-oct-6-enose (3), prepared [5] from D-galactose, was epoxidised with alkaline hydrogen peroxide to give a mixture of two isomers in the ratio 5 : 1. Column chromatography on silica gel resulted in total separation of the two nitro-epoxides. The preponderant isomer has been tentatively assigned the L-configuration (4) and the minor compound the D-configuration (5). These assignments are based on c.d. spectra, which show that stereochemically C-6 and C-7 in these products are mirror images, and on the configuration of the product of the reaction of compound (4) with benzylamine (Scheme 1).



(1) (2)

Treatment of the nitro-epoxide (4) with benzylamine in dimethylformamide (DMF) afforded only one benzylamino-ketone, 6-benzylamino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-octos-7-ulose (6). Reduction of compound (6) with sodium borohydride

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